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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/062,308	02/01/2002	David L. Rimm	YUA-001.01	2553

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FOLEY HOAG, LLP  
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EXAMINER

MAHATAN, CHANNING

ART UNIT	PAPER NUMBER
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1631

DATE MAILED: 12/18/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

**Office Action Summary**

Application No.

10/062,308

Applicant(s)

RIMM ET AL.

Examiner

Channing S. Mahatan

Art Unit

1631

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

- 1) ☐ Responsive to communication(s) filed on \_\_\_\_.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

- 4) ☒ Claim(s) 1-38 is/are pending in the application.
- 4a) Of the above claim(s) 33-38 is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 1-32 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_ are subject to restriction and/or election requirement.

**Application Papers**

- 9) ☒ The specification is objected to by the Examiner.
- 10) ☒ The drawing(s) filed on 01 February 2002 is/are: a) ☒ accepted or b) ☐ objected to by the Examiner.
- Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) ☐ The proposed drawing correction filed on \_\_\_\_ is: a) ☐ approved b) ☐ disapproved by the Examiner.
- If approved, corrected drawings are required in reply to this Office action.
- 12) ☐ The oath or declaration is objected to by the Examiner.

**Priority under 35 U.S.C. §§ 119 and 120**

- 13) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some \* c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- \* See the attached detailed Office action for a list of the certified copies not received.
- 14) ☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).
- a) ☐ The translation of the foreign language provisional application has been received.
- 15) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

**Attachment(s)**

- 1) ☒ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 2 Sheets.
- 4) ☐ Interview Summary (PTO-413) Paper No(s). \_\_\_\_.
- 5) ☐ Notice of Informal Patent Application (PTO-152)
- 6) ☐ Other: \_\_\_\_.

Art Unit: 1631

*ART UNIT DESIGNATION*

The Group and/or Art Unit designated for this application has changed. Applicants are hereby informed that future correspondence regarding this application should be directed to Group Art Unit 1631.

**Restriction/Election Requirement**

Restriction to one of the following inventions is required under 35 U.S.C. § 121:

Restriction to one of the following inventions is required under 35 U.S.C. § 121:

- I. Claims 1-32; drawn to a method of analyzing a cell with a biomarker, classified in class 702, subclass 19.
- II. Claims 33-38; drawn to a method of analyzing a plurality of spots, classified in class 702, subclass 20; class 435, subclasses 174/287.2.

The inventions are distinct, each from the other because:

The inventions of Groups I and II are unrelated. Inventions are unrelated if it can be shown that they are not disclosed as capable of use together and they have different modes of operation, different functions, or different effects (M.P.E.P. § 806.04, M.P.E.P. § 808.01). In the instant case the different inventions directed to products and methods having different functions, different effects, and different modes of operations. Group I is a method for analyzing a cell with a biomarker (i.e. selective staining). Group II is a method of analyzing spots (i.e. from a microarray). The above groups do not require aspects found distinctive within each group. For example, Group I does not require the spot analysis of Group II and Group II does require the selective staining method steps of Group I. Thus, Groups I and II have different functions, different effects (i.e. different results), and different modes of operation.

Art Unit: 1631

Because these inventions are distinct for the reasons given above, have acquired a separate status in the art because of their recognized divergent subject matter, restriction for examination purposes as indicated is proper.

Applicants are advised that the response to this requirement to be complete must include an election of the invention to be examined even though the requirement be traversed (37 C.F.R. § 1.143).

*TELEPHONE ELECTION*

During a telephone conversation with Beth Arnold on 06 November 2003 a provisional election was made without traverse to prosecute the invention of Group I, claims 1-32.

Affirmation of this election must be made by Applicants in replying to this Office action.

Claims 33-38 are withdrawn from further consideration by the examiner, 37 C.F.R. § 1.142(b), as being drawn to a non-elected invention.

*CLAIMS UNDER EXAMINATION*

Claims herein under examination are claims 1-32

**Claims Rejected Under 35 U.S.C. § 112 1<sup>st</sup> Paragraph**

The following is a quotation of the first paragraph of 35 U.S.C. § 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

*LACK OF ENABLEMENT*

Claims 11-29 are rejected under 35 U.S.C. § 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described

in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized in Ex parte Forman, 230 U.S.P.Q. 546 (B.P.A.I. 1986) and reiterated by the Court of Appeals in In re Wands, 8 U.S.P.Q. 2d 1400 at 1404 (C.A.F.C. 1988). The factors to be considered in determining whether undue experimentation is required include: (1) the quantity of experimentation necessary, (2) the amount or direction presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims. The Board also stated that although the level of skill in molecular biology is high, the results of experiments in genetic engineering are unpredictable. While all of these factors are considered, a sufficient amount for a *prima facie* case are discussed below.

Claims 11-29 are rejected under 35 U.S.C. § 112, first paragraph. It is acknowledged the claimed method analyzes a cell containing sample. However, absent is the intended goal that would be achieved through the implementation of the instantly claimed method. For instance, after “comparing the first and second images to identify pixel locations in the second image that are within the first cellular compartment”: 1) no output information is identified; 2) if an output is information is derived what is the output information intended to represent/what does one do with the output information? The claim as written Thus, one skilled in the art would not understand what the information means and what to do with the information after the generation

of the output without an intended goal. No guidance, direction, or examples are provided such that one of ordinary skill in the art would have known how to use the claimed invention.

**Claims Rejected Under 35 U.S.C. § 112 2<sup>nd</sup> Paragraph**

The following is a quotation of the second paragraph of 35 U.S.C. § 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 3, 4, and 6 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

*VAGUE AND INDEFINITE*

Claims 3 (line 2), 4 (line 1), and 6 (line 1) recites the term “associated” which is vague and indefinite. Applicants can resolve this issue by particularly pointing out the criteria/limitations the term “associated” is intended to encompass. Clarification of the metes and bounds, via clearer claim language, is requested.

**Claims Rejected Under 35 U.S.C. § 102**

The following is a quotation of the appropriate paragraphs of 35 U.S.C. § 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-13 and 30-32 are rejected under 35 U.S.C. § 102(b) as being anticipated by Bacus et al. (U.S. Patent Number 4,998,284).

Bacus et al. discloses a method and apparatus for use in performing automated classification of cell and other microscopic specimens (Abstract). The apparatus and techniques

Art Unit: 1631

provide: 1) alternative staining and analytical techniques for different cells, cytoplasm, and cell populations; 2) enhance image and color separation for greater distinguishment by the image processing equipment. The inventors describe various cell staining techniques (Columns 10-12). Figure 12 illustrates the method of measuring and analysis of DNA using the marking technique of the invention. First a slide containing control cell objects and specimen cell objects are stained by the alkaline phosphatase technique utilizing fast red dye (specific against the cytoplasmic antigen). Next the process slide is then stained by the Feulgen process, utilizing Thionin dye. After mounting the slide it is then positioned to provide a clear field on image monitor. The light level is then set and the platform is adjusted or traversed to control cell, or an image of a subpopulation of the control cell or cells appears on monitor. The image is that of the filtered image (red) showing only Feulgen stained areas. The amount of staining to determine the DNA index therein, for determination of the mass through optical density, is found by measuring the optical density of the control cells. The calibration is repeated to obtain an accurate measurement and assessment of the calibration and the process is repeated by iterating through the steps. The platform may be manually adjusted to another location to provide a second field of control cells. The peak of the optical density units is measured, converted into a DNA index, which index is stored in the computer memory. The DNA of the unknown cell sample is thereafter analyzed from specimen section slide, which has been positioned under the focal lens of the microscope by manual adjustment of platform. A cytoplasmic image of the specimen field may be obtained utilizing the blue filter and its boundary. Similarly, a DNA image of the specimen field is provided through the red filter and its boundary set. These filtered images are real-time images of the field and may be constantly updated through image

Art Unit: 1631

acquisition means of the system. The apparatus combines the two filtered images to mark the selected cells on image monitor while displaying the nuclear DNA area. The analysis program then proceeds to the classification step. In the classification mode, the image acquisition and combination ceases and a static or fixed image is projected on image monitor. The cells in the image on monitor are classified by type through an interactive process with an operator. Each cell is noted by the apparatus and the operator selects a classification for the separate cell using nuclear morphology and cytoplasmic markings of the combined image. Classified cells are then measured for the cell component, such as DNA content, and the results of the measurements may be displayed. This measurement display can be accommodated in several forms and with statistical analyses of the different classifications or combinations of such classifications. The measurement step can include more than the cells in a single field simply by iterating through the steps. The operator may manually move platform to another specimen field, and the marking and imaging steps may again be repeated as described above. The accumulated data in the measuring steps for the new cell populations is compiled with that of the previously developed cell population data. The display step noted in the above description can be delayed until a significant or required amount of data is accumulated, or display of each iteration may be provided at the option of the operator. In addition, the operator may elect to bypass setting the cytoplasm boundary and DNA boundary after they have been first set for a specimen image. Thus, Bacus et al. anticipates the claimed invention.

### **Claims Rejected Under 35 U.S.C. § 103**

The following is a quotation of 35 U.S.C. § 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

Art Unit: 1631

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

Claims 1-32 are rejected under 35 U.S.C. § 103(a) as being obvious over Bacus et al.

(U.S. Patent Number 4,998,284) taken in view of Garini et al. (U.S. Patent Number 6,165,734).

Bacus et al. is applied from above. However, Bacus et al. fails to disclose the utilization of more than two stains for cellular structure determination.

Garini et al. discloses A method of in situ analysis of a biological sample comprising the steps of (a) staining the biological sample with N stains of which a first stain is selected from the group consisting of a first immunohistochemical stain, a first histological stain and a first DNA ploidy stain, and a second stain is selected from the group consisting of a second immunohistochemical stain, a second histological stain and a second DNA ploidy stain, with provisions that N is an integer greater than three and further that (i) if the first stain is the first immunohistochemical stain then the second stain is either the second histological stain or the second DNA ploidy stain; (ii) if the first stain is the first histological stain then the second stain is either the second immunohistochemical stain or the second DNA ploidy stain; whereas (iii) if the first stain is the first DNA ploidy stain then the second stain is either the second immunohistochemical stain or the second histological stain; and (b) using a spectral data collection device for collecting spectral data from the biological sample, the spectral data collection device and the N stains are selected such that a spectral component associated with each of the N stains is collectable (Abstract). The inventors define the term histological stain as any colorant, reaction and/or associated reagents used to stain cells and tissues in association with cell components such as types of proteins (acidic, basic), DNA, RNA, lipids, cytoplasm

Art Unit: 1631

components, nuclear components, membrane components, etc. (Columns 37-38, lines 66-65 and 1-4, respectively).

Thus, it would have been obvious to one of skill in the art at the time of the invention to practice Bacus et al., method and apparatus for use in performing automated classification of cell and other microscopic specimens, with the multiple staining of Garini et al.. One would be motivated to characterize/identify other cellular components (i.e. nuclear, membrane, etc.) with the cell image as indicated by Bacus et al. (Column 29, lines 20-51).

*OBJECTION TO DISCLOSURE*

The disclosure is objected to because of the following informalities:

The specification on page 28, lines 1-2 states "...either polyclonal rabbit anticytokeratin (Zymed, So. San Francisco, CA) or rabbit anti-alpha-catenin (?)...", wherein it is unclear what Applicants refer to as "(?)". It is believed "(?)" refers to a corporation and location, however, it is unclear as to the corporation and its' location.

*INFORMATION DISCLOSURE STATEMENT*

The reference to the 'International Search Report' in the 'Information Disclosure Statement' filed 23 December 2002 was lined through because said reference is not publicly available.

**Appropriate correction is required.**

**No Claims Are Allowed.**

*INVENTORSHIP AMENDMENT*

Applicants are reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 C.F.R. §1.48(b) if one or more of the

Art Unit: 1631

currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a petition under 37 C.F.R. § 1.48(b) and by the fee required under 37 C.F.R. § 1.17(i).

*EXAMINER INFORMATION*

Papers related to this application may be submitted to Technical Center 1600 by facsimile transmission. Papers should be faxed to Technical Center 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notices published in the Official Gazette, 1096 OG 30 (November 15, 1988), 1156 OG 61 (November 16, 1993), and 1157 OG 94 (December 28, 1993) (See 37 C.F.R. § 1.6(d)). The CM1 Fax Center number is either (703) 872-9306.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Channing S. Mahatan whose telephone number is (703) 308-2380. The examiner can normally be reached on M-F (8:30-5:00).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael P. Woodward, Ph.D., can be reached on (703) 308-4028.

Any inquiry of a general nature or relating to the status of this application should be directed to Legal Instruments Examiner, Tina M. Plunkett, whose telephone number is (703) 305-3524 or to the Technical Center receptionist whose telephone number is (703) 308-0196.

Date:

December 11, 2003

Examiner Initials:

CSM

*Marianne P. Allen*  
MARIANNE P. ALLEN  
PRIMARY EXAMINER  
GROUP 1800  
12/11/03